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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Steven Neville Chatfield	Attorney Docket:	KCO1002US
Serial No.:	09/527,919	Group Art Unit:	1648
Filed:	March 17, 2000	Examiner:	Bao Qun Li
For:	HEPATITIS B VIRUS POLYPEPTIDES		

APPEAL BRIEF

Mail Stop Appeal Brief-
Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

1. Real Party in Interest

The subject application is assigned of record to Medeva Europe Limited, Medeva House, Regent Park, Kingston Road, Leatherhead, Surrey, KT22 7PQ, United Kingdom. Medeva Europe Limited has changed its name to Celltech Pharma Europe Limited, which has an address of 208 Bath Road, Slough, Berkshire, SL1 3WE, United Kingdom. A change of name to Celltech Pharma Europe Limited has been submitted separately.

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Date: June 10, 2003 **Signature:** Jodi Jung

Name: Jodi Jung

2. Related Appeals and Interferences

There are no known related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

3. Status of Claims

Claims 35 to 38, 40 to 44, and 46 are pending in this application. Claims 1 to 34, 39, and 45 have been cancelled. The rejection of claims 35 to 38, 40 to 44, and 46 is appealed.

4. Status of Amendments

In an amendment filed on November 8, 2002, claims 39 and 45 were cancelled and claims 35, 38, 41, and 44 were amended. The Examiner confirmed that these amendments would be entered on appeal in the December 18, 2002 Office Action.

5. Summary of Invention

The present invention provides polypeptides and immunogenic compositions that may be used in the prevention or treatment of hepatitis B viral infections. See page 2, lines 8 and 9, of the specification.

As recited in claim 35, the invention provides a fusion polypeptide comprising (i) tetanus toxin fragment C, fused to (ii) a polypeptide consisting of at least 6 contiguous amino acids of sequence of pre-S1 of hepatitis B virus (HBV), and the fusion polypeptide induces antibody that recognizes pre-S1 of HBV. See page 3, line 13, to page 4, line 3, of the specification. As recited in claim 41, the invention also provides an immunogenic composition comprising a pharmaceutically acceptable carrier or diluent and the fusion polypeptide of claim 35. See page 8, line 5, to page 9, line 5, of the specification.

In the embodiments of claims 36 and 42, the fusion polypeptide comprises at least 20 contiguous amino acids of the sequence of pre-S1. See page 3, line 27, to page 4, line

3, of the specification. In the embodiments of claims 37 and 43, the fusion polypeptide comprises amino acids 21 to 47 of pre-S1. See page 4, lines 1 to 3, of the specification. In the embodiments of claims 38 and 44, the tetanus toxin fragment C and the polypeptide consisting of at least 6 contiguous amino acids of sequence of pre-S1 of HBV are joined by a hinge linker. See page 4, line 25, to page 5, line 25, of the specification. In the embodiments of claims 40 and 46, the fusion polypeptide comprises full length tetanus toxin fragment C. See page 3, lines 16 to 19, of the specification.

6. Issues

Whether claims 35 to 38, 40 to 44, and 46 are unpatentable under 35 U.S.C. § 103(a) over Mimms et al. (EP-A-0 389 983), Khan et al. (WO 94/03615), and Shi et al. (Vaccine 1995, Vol. 13, pp. 933-937). Copies of each of these references are enclosed.

7. Grouping of Claims

Claims 35 to 38, 40 to 44, and 46 stand or fall together.

8. Argument

Rejection of Claims 35 to 38, 40 to 44, and 46 Under 35 U.S.C. § 103(a) Over Mimms et al., Khan et al., and Shi et al.

Claims 35 to 38, 40 to 44, and 46 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Mimms et al. (EP-A-0 389 983), Khan et al. (WO 94/03615) and Shi et al. (Vaccine 1995, Vol. 13, pp. 933-937).

The Examiner has suggested that Khan et al. explicitly teaches that tetC has been extensively used as an adjuvant and that a recombinant antigen made by tetC has good and enhanced immunogenicity. However, the passages referred to by the Examiner at page 3, line 4, to page 4, line 8, refer to the immunogenicity of tetC *per se*, not to its

ability to act as a carrier protein in a fusion polypeptide that induces antibody that recognizes the fused peptide. In fact, the passages mentioned by the Examiner highlight the potential problems of generating such fusion proteins. See, for example, page 3, lines 10 to 24. Khan suggests that "*fusing two proteins together often leads to an incorrectly folded chimaeric protein which no longer retains the properties of the individual components.*" Page 3, lines 10 to 12. Khan et al. indicates that a solution to this general problem has been found, but only actually goes on to demonstrate immunogenicity with a small number of specific epitopes. Khan et al. further acknowledges at page 25, lines 17 to 19, that the efficacy of such fusion proteins is by no means certain, stating that "[*t*]*he antibody response to TetC was not the same in all groups; the addition of C-terminal fusions to TetC clearly modified the response.*"

The Examiner also refers to the mention of hepatitis B in Khan et al. The Examiner suggests that Khan et al. refers to "several viral antigens", including hepatitis B, as being suitable for making a fusion protein with tetC. However, the passage referred to by the Examiner at page 5, line 10, to page 6, line 4, is simply a laundry list of a large number of viral antigenic sequences. This is then followed by a similarly long list of antigens derived from bacteria. There is no suggestion that these are any more than arbitrary lists of antigens to which one might wish to stimulate an immune response. There is no evidence in Khan et al. to suggest that it might actually be possible to induce such a response using a fusion protein of tetC with any of the numerous antigens. Further, no specific antigenic sequences are mentioned. The list simply refers to "hepatitis A or B virus." The skilled person would not be able to derive from Khan et al. what would or would not be a suitable hepatitis antigen to include in such a fusion protein.

There is therefore no evidence in Khan et al. to suggest that the tetC fusion protein system would be effective for the pre-S1 antigen recited in the instant claims. Indeed, Khan et al. teaches the skilled person that the antibody response to such fusion proteins is

highly variable. There would therefore be no expectation of success using a fusion peptide according to the present invention.

The Examiner has suggested that because Mimms et al. teaches several epitopes of HBV pre-S1 protein as a subunit antigen able to induce an immune response, it would be obvious to produce a fusion polypeptide of the present invention by combining the teachings of Khan et al. and Mimms et al. However, the test for obviousness over a combination of references such as this should involve a consideration of whether it was obvious to make that combination in the first place. As explained in the USPTO Manual of Patent Examining Procedure:

> "[*T*]*here must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine reference teachings. The Federal Circuit has produced a number of decisions overturning obviousness suggestions due to a lack of suggestion in the prior art of the desirability of combining references. . . .*" (MPEP § 2145, X.C.).

> "*The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a prima facie case of obviousness was held improper.*" (MPEP § 2143.01, first paragraph, referring to *In re Rouffet*).

> "*Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art.*" (MPEP § 2143.01, third paragraph).

> *"The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination."* (MPEP § 2143.01, eighth paragraph).

In the present case, there would have been no obvious reason why a skilled person would have focussed simultaneously and specifically on the disclosure relating to fragment C in Khan et al. and at the disclosure relating to specific pre-S1 fragments in Mimms et al. We respectfully point out that the Examiner has not suggested any such reason and that, as set forth in the parts of the MPEP quoted above, the rejection is therefore not properly supported. As submitted previously, there are a large number of possible carrier proteins that could be used, and a large number of specific antigens which could be combined with each carrier protein. See the Declaration of Dr. Mark Page of April 9, 2002. The skilled person would have no motivation to make this particular combination of features from within the Khan et al. and Mimms et al. references. As explained above, Khan et al. teaches the skilled person that the antibody response to such fusion proteins is highly variable and difficult to predict.

The Examiner has further referred to Shi et al. in support of the arguments and refers to the disclosure in Shi et al. of fusion proteins comprising cholera toxin B and HBV subunit antigen. Shi et al. does not teach the combination of tetC and HBV pre-S1. The person of ordinary skill in the art would not combine the teaching of Shi et al. with that of Khan et al. as they refer to different carrier proteins. A combination of Mimms et al. with Shi et al. would similarly not lead someone of ordinary skill in the art to the present invention. Rather it would lead them to include the specific pre-S1 fragments of Mimms et al. into the cholera toxin B fusion protein of Shi et al.

Further, the particular combination claimed in the present application does achieve unexpected results. As explained in the Declaration of Mark Page of April 9, 2002, the

Examples in the present application show that an unexpectedly high antibody response is induced against pre-S by the fusion proteins that are the subject of the application. The Examiner appears to have overlooked this.

For example, the results presented in Figure 3b show that, seven days after a booster dose, the fusion proteins induced a good antibody titer against a pre-S1 peptide. The titer is of the same order of magnitude as that against the fragment C component of the proteins (see Figure 2b). These results would not have been expected from a reading of Shi et al. and the other references mentioned by the Examiner. Indeed, Shi et al. teaches against any expectation of such results. Shi et al. teaches that an extremely low antibody titer is to be expected. This is clear from, for example, Figure 7 at page 936 of Shi et al. This figure shows that the peak antibody titer against cholera toxin B alone was about 5000, whereas the peak titer against pre-S2 was only about 140. The peak anti-pre-S2 titer was therefore about 35 times less than the peak anti-cholera toxin B titer. This contrasts with the examples of the present application, where the titer against a pre-S1 peptide from the fusion proteins (see Figure 3B and page 14) is of the same order of magnitude as that against the fragment C component of the proteins (see Figure 2B and page 14).

The Manual of Patent Examining Procedure states in Section 716.02(a), second paragraph, that:

> "*Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shared with the prior art, can rebut prima facie obviousness.*"

In light of Shi et al. there would have been no expectation of success in fusing pre-S sequences to carrier proteins. This is supported by the passage at page 25, lines 17 to 19, of Khan et al. which, as explained above, suggests that the antibody response depends

upon the particular C-terminal fusion peptide chosen and that only some such fusions would be capable of stimulating a suitable antibody response.

There was therefore unpredictability in the art at the filing date. In particular, it would not have been possible to predict in advance whether any specific fusion protein would be capable of exhibiting enhanced immunogenicity. The Examiner has previously stated that "*it is unpredictable that each . . . designed fusion protein is able to produce an enhanced immunity.*" July 8, 2002 Final Office Action, page 4, lines 14 and 15. It is therefore submitted that it cannot have been obvious that the claimed fusion proteins would themselves exhibit an enhanced immunogenicity.

For the foregoing reasons, Applicant respectfully requests reversal of the rejection of claims 35 to 38, 40 to 44, and 46 under 35 U.S.C. § 103(a).

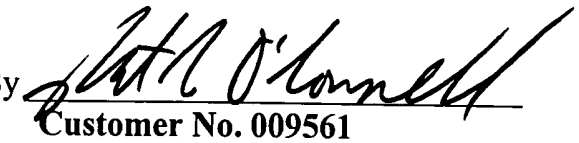
9. Appendix

The appealed claims are presented in the attached appendix.

Please charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 16-2312. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our deposit account.

Respectfully submitted,

Dated: June 10, 2003

By 

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Appendix

35. A fusion polypeptide comprising

(i) tetanus toxin fragment C, fused to

(ii) a polypeptide consisting of at least 6 contiguous amino acids of sequence of pre-S1 of hepatitis B virus (HBV),

wherein the fusion polypeptide induces antibody that recognizes pre-S1 of HBV.

36. A fusion polypeptide according to claim 35 which comprises at least 20 contiguous amino acids of the sequence of pre-S1.

37. A fusion polypeptide according to claim 35 which comprises amino acids 21 to 47 of pre-S1.

38. A fusion polypeptide according to claim 35 wherein the tetanus toxin fragment C and the polypeptide consisting of at least 6 contiguous amino acids of sequence of pre-S1 of HBV are joined by a hinge linker.

40. A fusion polypeptide according to claim 35 which comprises full length fragment C.

41. An immunogenic composition comprising a pharmaceutically acceptable carrier or diluent and a fusion polypeptide comprising

(i) tetanus toxin fragment C, fused to

(ii) a polypeptide consisting of at least 6 contiguous amino acids of sequence of pre-S1 of hepatitis B virus (HBV),

wherein the composition induces antibody that recognizes pre-S1 of HBV.

42. An immunogenic composition according to claim 41 wherein the fusion polypeptide comprises at least 20 contiguous amino acids of the sequence of pre-S1.

43. An immunogenic composition according to claim 41 wherein the fusion polypeptide comprises amino acids 21 to 47 of pre-S1.

44. An immunogenic composition according to claim 41 wherein the tetanus toxin fragment C and the polypeptide consisting of at least 6 contiguous amino acids of sequence of pre-S1 of HBV are joined by a hinge linker.

46. An immunogenic composition according to claim 41 wherein the fusion polypeptide comprises full length tetanus toxin fragment C.